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=> d his

     (FILE 'HOME' ENTERED AT 14:14:37 ON 07 JUN 2001)

     INDEX 'ADISALERTS, ADISINSIGHT, AGRICOLA, ANABSTR, AQUASCI, BIOBUSINESS,
     BIOCOMMERCE, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA, CANCERLIT,
     CAPLUS, CEABA-VTB, CEN, CIN, CONFSCI, CROPB, CROPU, DDFB, DDFU, DGENE,
     DRUGB, DRUGLAUNCH, DRUGMONOG2, DRUGNL, ...' ENTERED AT 14:16:21 ON 07
JUN
     2001
                  SEA (TRIFLUORO-2-HYDROXY-2-METHYLPROPIONIC ACID) OR
(TRIFLUORO-
                 ---------
                  2   FILE ADISINSIGHT
                  5   FILE BIOSIS
                  3   FILE BIOTECHABS
                  3   FILE BIOTECHDS
                  4   FILE BIOTECHNO
                 16   FILE CAPLUS
                  1   FILE CEABA-VTB
                  4   FILE DDFU
                  4   FILE DRUGU
                  1   FILE EMBAL
                 35   FILE EMBASE
                  2   FILE ESBIOBASE
                  2   FILE GENBANK
                  6   FILE MEDLINE
                  1   FILE PASCAL
                  7   FILE SCISEARCH
                  1   FILE SYNTHLINE
                  7   FILE TOXLIT
                  6   FILE USPATFULL
                  4   FILE WPIDS
                  4   FILE WPINDEX
L1                 QUE (TRIFLUORO-2-HYDROXY-2-METHYLPROPIONIC ACID) OR
(TRIFLUORO-
                 ---------

     FILE 'EMBASE, CAPLUS, SCISEARCH, TOXLIT' ENTERED AT 14:25:28 ON 07 JUN
     2001
L2            10 S L1 AND (BIOSYNTH? OR SYNTHE?)
L3             8 DUP REM L2 (2 DUPLICATES REMOVED)
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FILE 'REGISTRY' ENTERED AT 14:31:48 ON 07 JUN 2001

STRUCTURE FILE UPDATES: 6 JUN 2001 HIGHEST RN 339983-69-6
DICTIONARY FILE UPDATES: 6 JUN 2001 HIGHEST RN 339983-69-6

TSCA INFORMATION NOW CURRENT THROUGH January 11, 2001

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Structure search limits have been increased. See HELP SLIMIT for details.

=> e (R)-3,3,3-trifluoro-2-hydroxy-2-methylpropionic acid/CN

```
E1            1      (R)-3,3'-DIPHENYL-1,1'-BINAPHTHALENE-2,2'-DIOL/CN
E2            1      (R)-3,3,3-TRIFLUORO-1,2-PROPANEDIOL/CN
E3            0 --> (R)-3,3,3-TRIFLUORO-2-HYDROXY-2-METHYLPROPIONIC ACID/CN
E4            1      (R)-3,3,3-TRIFLUORO-2-METHOXY-2-PHENYLPROPANOYL CHLORIDE/CN
E5            1      (R)-3,3,5-TRIMETHYLCYCLOHEXANONE/CN
E6            1      (R)-3,3,5-TRIMETHYLPYRROLIDIN-2-ONE/CN
E7            1      (R)-3,3-BIS(4-FLUOROPHENYL)OXIRANECARBOXALDEHYDE/CN
E8            1      (R)-3,3-DIMETHYL-1,2-BUTANEDIOL/CN
E9            1      (R)-3,3-DIMETHYL-1-PIPERIDINO-2-BUTANOL/CN
E10           1      (R)-3,3-DIMETHYL-2-BUTANAMINE/CN
E11           1      (R)-3,3-DIMETHYL-2-BUTANOL/CN
E12           1      (R)-3,3-DIMETHYL-2-METHYLAMINOBUTANE/CN
```

=> e (R)-3,3,3-trifluoro-2-hydroxy-2-methylpropionamide/CN

```
E1            1      (R)-3,3'-DIPHENYL-1,1'-BINAPHTHALENE-2,2'-DIOL/CN
E2            1      (R)-3,3,3-TRIFLUORO-1,2-PROPANEDIOL/CN
E3            0 --> (R)-3,3,3-TRIFLUORO-2-HYDROXY-2-METHYLPROPIONAMIDE/CN
E4            1      (R)-3,3,3-TRIFLUORO-2-METHOXY-2-PHENYLPROPANOYL CHLORIDE/CN
E5            1      (R)-3,3,5-TRIMETHYLCYCLOHEXANONE/CN
E6            1      (R)-3,3,5-TRIMETHYLPYRROLIDIN-2-ONE/CN
E7            1      (R)-3,3-BIS(4-FLUOROPHENYL)OXIRANECARBOXALDEHYDE/CN
E8            1      (R)-3,3-DIMETHYL-1,2-BUTANEDIOL/CN
E9            1      (R)-3,3-DIMETHYL-1-PIPERIDINO-2-BUTANOL/CN
E10           1      (R)-3,3-DIMETHYL-2-BUTANAMINE/CN
E11           1      (R)-3,3-DIMETHYL-2-BUTANOL/CN
E12           1      (R)-3,3-DIMETHYL-2-METHYLAMINOBUTANE/CN
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=> d l3 ibib ab 1-8

L3 ANSWER 1 OF 8 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 1
ACCESSION NUMBER: 2001177428 EMBASE
TITLE: Low levels of K(ATP) channel activation decrease excitability and contractility of urinary bladder.
AUTHOR: Petkov G.V.; Heppner T.J.; Bonev A.D.; Herrera G.M.; Nelson M.T.
CORPORATE SOURCE: M.T. Nelson, Dept. of Pharmacology, College of Medicine, University of Vermont, Burlington, VT 05405, United States. nelson@salus.med.uvm.edu
SOURCE: American Journal of Physiology - Regulatory Integrative and Comparative Physiology, (2001) 280/5 49-5 (R1427-R1433). Refs: 26
ISSN: 0363-6119 CODEN: AJPRDO
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Activation of ATP-sensitive potassium (K(ATP)) channels can regulate smooth muscle function through membrane potential hyperpolarization. A critical issue in understanding the role of K(ATP) channels is the relationship between channel activation and the effect on tissue function.
Here, we explored this relationship in urinary bladder smooth muscle (UBSM) from the detrusor by activating K(ATP) channels with the **synthetic** compounds N-(4-benzoylphenyl)-3,3,3-**trifluoro-2-hydroxy-2-methylpropionamide** (ZD-6169) and levcromakalim. The effects of ZD-6169 and levcromakalim on K(ATP) channel currents in isolated UBSM cells, on action potentials, and on related phasic contractions of isolated UBSM strips were examined. ZD-6169 and levcromakalim at 1.02 and 2.63 .mu.M, respectively, caused half-maximal activation (K(1/2)) of K(ATP) currents in single UBSM cells (see Heppner TJ, Bonev A, Li JH, Kau ST, and Nelson MT. Pharmacology 53: 170-179, 1996). In contrast, much lower concentrations (K(1/2) = 47 nM for ZD-6169 and K(1/2) = 38 nM for levcromakalim) caused inhibition of action potentials and phasic contractions of UBSM. The results suggest that activation of <1% of K(ATP) channels is sufficient to inhibit significantly action potentials and the related phasic contractions.

L3 ANSWER 2 OF 8 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001120120 EMBASE
TITLE: N-acyl-1,2,3,4a,5,10b-hexahydro-[1]benzopyrano-[3,4-b][1,4]oxazine-9- carbonitriles as bladder-selective potassium channel openers.
AUTHOR: Chiu H.-I.; Lin Y.-C.; Cheng C.-Y.; Tsai M.-C.; Yu H.-C.
CORPORATE SOURCE: C.-Y. Cheng, Institute of Pharmaceutical Sciences, College of Medicine, National Taiwan University, Taipei 10018, Taiwan, Province of China. cyc@ha.mc.ntu.edu.tw
SOURCE: Bioorganic and Medicinal Chemistry, (2001) 9/2 (383-393). Refs: 31

ISSN: 0968-0896 CODEN: BMECEP
PUBLISHER IDENT.: S [redacted]8-0896(00)00260-1
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 028 Urology and Nephrology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Optically active N-acyl-5,5-dimethyl-1,2,3,4a,5,10b-hexahydro-[1]benzopyrano[3,4-b][1,4] oxazine-9-carbonitriles 2-22 were **synthesized** as rigid analogues of cromakalim. The (4aR,10bR)-N-benzoyl derivative (-)-11 was identified as a bladder-selective KCO (IC(50, bladder)=8.2 .mu.M, IC(50, portal vein)=34.5 .mu.M). Among the analogues of 11 with substitution on the benzoyl moiety, the 3-methyl analogue (-)-14 showed highly potent and selective activity at portal vein (IC(50, bladder)=279 .mu.M, IC(50, portal vein)=0.54 .mu.M). The 4-bromo analogue (-)-19 (IC(50, bladder)=2.0 .mu.M, IC(50, portal vein)=8.1 .mu.M) and the 4-hydroxy analogue (-)-21 (IC(50, bladder)=3.8 .mu.M, IC(50, portal vein)=75 .mu.M) showed enhanced activity at the bladder, while maintaining unprecedented bladder selectivity in vitro. The N-benzenesulfonyl analogue (-)-22, a bioisoster of (-)-11, showed similar activity at the bladder with enhanced selectivity (IC(50, bladder)=11.6 .mu.M, IC(50, portal vein)=120 .mu.M). .COPYRGT. 2001 Elsevier Science Ltd.

L3 ANSWER 3 OF 8 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000237543 EMBASE
TITLE: Potassium channel openers as potential therapeutic weapons in ion channel disease.
AUTHOR: Lawson K.
CORPORATE SOURCE: Dr. K. Lawson, Biomedical research Centre, Sheffield Hallam University, City Campus, Sheffield S1 1WB, United Kingdom. k.lawson@shu.ac.uk
SOURCE: Kidney International, (2000) 57/3 (838-845).
Refs: 28
ISSN: 0085-2538 CODEN: KDYIA5
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The opening of potassium (K+) channels, causing hyperpolarization of the cell membrane, is a physiological means of decreasing cell excitability. Thus, drugs with this properly will demonstrate a broad clinical potential. The identification of **synthetic** molecules that evoke physiological responses (for example smooth muscle relaxation) by the opening of K+ channels led to a new direction in the pharmacology of ion channels. The term 'potassium channel openers' was initially associated with a group of chemically diverse agents (for example, cromakalim, pinacidil, nicorandil) that evoke K+ efflux through adenosine 5'-triphosphate (ATP)-sensitive K+ channels (K(ATP)). This finding initiated a search to identify molecules that specifically open other K+ channel subtypes (for example large conductance calcium-activated K+ channels [BK(Ca)]). K+ channel opening properties have been demonstrated in a diverse range of **synthetic** chemical structures and endogenous substances. Second generation K(ATP) channel openers (K(ATP)COs) demonstrate heterogeneous pharmacology indicative of independent sites of action for the different agents. Successful cloning of the K(ATP) channel has shed light on the heterogeneity of the structure

targeted by K(ATP)COs. Expression of the actions of K(ATP)COs involves three isoforms of the sulfonylurea (SUR) receptor which forms the .beta. subunit of the K(ATP) channel). The distribution of the SUR isoforms (and potential of identifying new isoforms) provides unique targets for the development of selective K(ATP)COs giving focused therapeutic approaches to clinical conditions for example cardiac ischemia, urinary incontinence, neurodegeneration, obesity and autoimmune diseases. BK(Ca) channels are found in a diverse array of tissues and due to voltage and Ca sensitivity may work as a negative feedback process. A variety of small **synthetic** molecules (for example, NS004, fenamates) and natural product-derived compounds (DHS-I, maxikdiol) have been identified as selective BK(Ca) channel openers which should have a profound impact in controlling diseases. The discovery of numerous variants of the .alpha. subunit (ion conductance pore) and .beta. subunit (contributes biophysical and pharmacological properties) complex of the BK(Ca) channel gives potential to target specific tissues with selective openers. Little is known, however, about the site(s) of interaction of openers of these channels. The discovery of K+ channel subtype-specific openers and their evaluation in different diseases will determine the degree to which these channels (K(ATP), BK(Ca)), or their isoforms, represent realistic therapeutic targets. Drugs already marketed that open K+ channels were discovered empirically, and most have serious safety and efficacy problems. New scientific methods, utilizing molecular insight, are implicating K+ channel dysfunction in numerous disease states and are identifying new targets for the future generation of K+ channel opening drugs.

L3 ANSWER 4 OF 8 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2000240678 EMBASE

TITLE: Pharmacological and molecular analysis of ATP-sensitive K+ channels in the pig and human detrusor.

AUTHOR: Buckner S.A.; Milicic I.; Daza A.; Davis-Taber R.; Scott V.E.S.; Sullivan J.P.; Brioni J.D.

CORPORATE SOURCE: S.A. Buckner, Neurological/Urological Dis. Res., Pharmaceutical Products Division, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064-6118, United States. steven.a.buckner@abbott.com

SOURCE: European Journal of Pharmacology, (21 Jul 2000) 400/2-3 (287-295).
Refs: 41
ISSN: 0014-2999 CODEN: EJPHAZ

PUBLISHER IDENT.: S 0014-2999(00)00388-5

COUNTRY: Netherlands

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 002 Physiology
028 Urology and Nephrology
030 Pharmacology
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB The pharmacological and molecular properties of ATP-sensitive K+ channels present in pig detrusor smooth muscle were investigated. In isolated pig detrusor strips, ATP-sensitive K+ channel openers inhibited contractions elicited by low frequency field-stimulation in a concentration-dependent manner. The inhibitory effects of P1075 [N-cyano-N'-(1,1-dimethylpropyl)-N''-3-pyridylguanidine] were attenuated by glyburide with a pA2 value of 7.38 (slope=1.08). The potency of the inhibitory effects of the K+ channel openers on the field-stimulated contractions correlated well with those evoked by the muscarinic receptor agonist, carbachol (r=0.93) and furthermore, to relaxation of the pre-contracted (25 mM potassium chloride, KCl) human detrusor (r=0.95). Reverse transcriptase polymerase chain reaction (RT-PCR) analysis showed the presence of mRNA for sulfonylurea receptors SUR1 and SUR2B in both pig and human detrusor.

Considering the s' larities in the molecular and pharmacological profile of ATP-sensitive channels between the pig and t[redacted] human detrusor, it is concluded that the pig detrusor may serve as a suitable in vitro model for the evaluation of novel K+ channel openers with potential use in urological disorders in humans. Copyright (C) 2000 Elsevier Science B.V.

L3 ANSWER 5 OF 8 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999358112 EMBASE
TITLE: YM-905. Treatment of urinary incontinence muscarinic M3 antagonist.
AUTHOR: Mealy N.; Castaner J.
CORPORATE SOURCE: N. Mealy, Prous Science, P.O. Box 540, 08080 Barcelona, Spain
SOURCE: Drugs of the Future, (1999) 24/8 (871-874).
Refs: 7
ISSN: 0377-8282 CODEN: DRFUD4
COUNTRY: Spain
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 028 Urology and Nephrology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English

L3 ANSWER 6 OF 8 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999197380 EMBASE
TITLE: (3'S,4'R)-N-(6-cyano-3,4-dihydro-2,2-dimethyl-3-hydroxy-2H-1-benzopyran- 4-yl)-2-hydroxy-2-trifluoromethylpropamides as potassium channel openers+.
AUTHOR: Chiu H.-I.; Cheng C.-Y.
CORPORATE SOURCE: C.-Y. Cheng, Institute of Pharmaceutical Sciences, College of Medicine, National Taiwan University, Taipei 10018, Taiwan,Province of China
SOURCE: Chinese Pharmaceutical Journal, (1999) 51/1 (87-92).
Refs: 7
ISSN: 1016-1015 CODEN: CYHCEX
COUNTRY: Taiwan,Province of China
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Based on a combination of the structural features of lemakalim and ZD6169, (2S,3'S,4'R)-N-(6-cyano-3,4-dihydro-2,2-dimethyl-3-hydroxy-2H-1-benzopyran-4-yl)-2-hydroxy-2-trifluoromethylpropamides ((-)-6) and its C-2 epimer (+)-7 were **synthesized** from (3S,4R)-6-cyano-3,4-epoxy-3,4-dihydro- 2,2-dimethyl-2H1-benzopyran ((-)-3). Compound 6, which has the same configuration (S) at C-2 as that of ZD6169, showed significant potassium channel activation activity on rat portal vein and rat bladder detrusor strips (EC50's = 2.5 and 5.4 .mu.M respectively); while its epimer 7 was only weakly active.

L3 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:66005 CAPLUS
DOCUMENT NUMBER: 128:153206
TITLE: Manufacture of (S)- or (R)-3,3,3-**trifluoro-2-hydroxy-2-methylpropionic acid** from propionamides with amidohydrolase **synthesizing** microorganisms
INVENTOR(S): Brieden, Walter; Naughton, Andrew; Robins, Karen; Shaw, Nicholas; Tinschert, Andreas; Zimmermann,

Thomas; et al.
PATENT ASSIGNEE(S): Lonza A.-G., Switz.; Brieden, [redacted]ter; Naughton, Andrew; Robins, Karen; Shaw, Nicholas
SOURCE: PCT Int. Appl., 68 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9801568	A2	19980115	WO 1997-EP3670	19970710
WO 9801568	A3	19980219		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2259954	AA	19980115	CA 1997-2259954	19970710
AU 9741137	A1	19980202	AU 1997-41137	19970710
EP 938584	A2	19990901	EP 1997-938817	19970710
R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, NL, SE, PT, IE, FI				
JP 2000513942	T2	20001024	JP 1998-504811	19970710

PRIORITY APPLN. INFO.: CH 1996-1723 A 19960710
CH 1997-500 A 19970303
WO 1997-EP3670 W 19970710

AB New microorganisms capable of using racemic or optically active 3,3,3-**trifluoro-2-hydroxy-2-methylpropionamide** (2,2-HTFMPA)as sole source of nitrogen are described for use in the manuf. of (S) - or (R)-3,3,3-**trifluoro-2-hydroxy-2-methylpropionic acid** from the trifluoroacetoacetic ester. The microorganisms have a new amidase that can catalyze the hydrolysis of the amide. The first three process steps are chem., the fourth process step microbiol. Microorganisms from the genera Klebsiella, Rhodococcus, Arthrobacter, Bacillus, and Pseudomonas were identified as useful in the process by screening for racemic 2,2-HTFMPA utilization. Utilizers were then screened for stereospecificity of utilization. The S-amidohydrolase gene (sad) of Klebsiella oxytoca was cloned by screening with amino acid sequence-derived probes.

L3 ANSWER 8 OF 8 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998018563 EMBASE
TITLE: The overactivity bladder: Pharmacologic basis of drug treatment.
AUTHOR: Andersson K.-E.; Cardozo L.; Malone-Lee J.; Levin R.M.; Abram P.; Wein A.J.
CORPORATE SOURCE: Prof. K.-E. Andersson, Department of Clinical Pharmacology,
Lund University Hospital, 5-221 85 Lund, Sweden
SOURCE: Urology, (1997) 50/6 SUPPL. A (74-89).
Refs: 107
ISSN: 0090-4295 CODEN: URGYAZ
PUBLISHER IDENT.: S 0090-4295(97)00595-5
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 028 Urology and Nephrology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Objectives. To provide an overview of the basis for drug treatment of the overactive bladder. Methods. Published information is evaluated. Results.

The causes of bladder overactivity are not known, but theoretically, increased afferent activity, decreased inhibitory control in the central nervous system (CNS) or peripheral ganglia, and increased sensitivity of the detrusor to efferent stimulation may be involved. Several CNS transmitters can modulate voiding, but few useful drugs with a defined CNS site of action have been developed. Drugs that stimulate .gamma.-aminobutyric acid receptors are used clinically. Potentially, drugs affecting opioid, 5-hydroxytryptamine, norepinephrine, dopamine, and glutamatergic receptors and mechanisms can be developed, but a selective action on the lower urinary tract may be difficult to obtain. Traditionally, drugs used for treatment of bladder overactivity have had a peripheral site of action, mainly efferent neurotransmission or the detrusor itself. Antimuscarinic drugs, .beta.-adrenoceptor agonists, .alpha.- adrenoceptor antagonists, drugs affecting membrane channels, prostaglandin **synthetase** inhibitors, and several other agents have been used with limited success. New information on the a-adrenoceptor and muscarinic receptor subtypes in the human detrusor has emerged and may be the basis for the development of new compounds with effects on bladder overactivity. Decreasing afferent activity seems an attractive therapeutic approach, and drugs affecting afferent nerves by causing release of tachykinins, such as capsaicin and analogs, as well as agents blocking tachykinin receptors, may be of therapeutic interst. Conclusions. New drugs, specifically designed for the treatment of bladder overactivity, are desirable.